

FORM PTO 1390
(REV 5-93)

US DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY DOCKET NO.
2000 0436ATRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 USC 371U.S. APPLICATION NO.
(if known, see 37 CFR 1.5)
NEW
09/529882International Application No.
PCT/JP99/04483International Filing Date
August 20, 1999Priority Date Claimed
August 21, 1998Title of Invention
AQUEOUS LIQUID PHARMACEUTICAL COMPOSITIONApplicant(s) For DO/EO/US
Shinichi YASUEDA and Katsuhiro INADA

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. This is a **FIRST** submission of items concerning a filing under 35 USC 371.
2. This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 USC 371.
3. This is an express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).
4. A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. A copy of the International Application as filed (35 USC 371(c)(2))
 - a. is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. has been transmitted by the International Bureau.
 - c. is not required, as the application was filed in the United States Receiving Office (RO/US).
6. A translation of the International Application into English (35 USC 371(c)(2)).
7. Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3)).
 - a. are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. have been transmitted by the International Bureau.
 - c. have not been made; however, the time limit for making such amendments has NOT expired.
 - d. have not been made and will not be made.
8. A translation of the amendments to the claims under PCT Article 19 (35 USC 371(c)(3)).
9. An executed oath or declaration of the inventor(s) (35 USC 371(c)(4)).
10. A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 USC 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. A **FIRST** preliminary amendment.
 - A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. A substitute specification.
15. A change of power of attorney and/or address letter.
16. Other items or information: (a) PCT Request; (b) Forms PCT/IB/301, 304 and 308; (c) First page of published international application; and (d) International Search Report

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) NEW 09/529882		INTERNATIONAL APPLICATION NO. PCT/JP99/04483		ATTORNEY DOCKET NO. 2000 0436A	
				CALCULATIONS	PTO USE ONLY
17. [X] The following fees are submitted					
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):					
<input checked="" type="checkbox"/> Search Report has been prepared by the EPO or JPO \$840.00 <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) \$670.00 <input type="checkbox"/> No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) \$690.00 <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$970.00 <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-33(4) \$ 96.00					
ENTER APPROPRIATE BASIC FEE AMOUNT = \$840.00					
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).					
Claims	Number Filed	Number Extra	Rate		
Total Claims	11 - 20 =	0	X \$18.00	\$	
Independent Claims	4 - 3 =	1	X \$78.00	\$78.00	
Multiple dependent claim(s) (if applicable)			+ \$260.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$918.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)					
SUBTOTAL =				\$918.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).					
TOTAL NATIONAL FEE =				\$918.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (\$40 per property).					
TOTAL FEES ENCLOSED =				\$958.00	
				Amount to be refunded:	\$
				charged:	\$

09/529882

422 Rec'd PCT/PTO 21 APR 2000

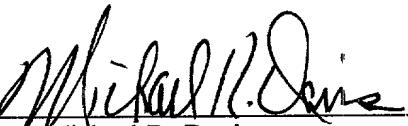
- a. A check in the amount of \$958.00 to cover the above fees is enclosed.
- b. Please charge my Deposit Account No. 23-0975 in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0975. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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By 
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THE COMMISSIONER IS AUTHORIZED
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2000_0436A

April 21, 2000
MRD/sls

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Shinichi YASUEDA et al. : Attn: BOX PCT

Serial No. NEW : Docket No. 2000_0436A

Filed April 21, 2000 :

AQUEOUS LIQUID PHARMACEUTICAL :

COMPOSITION

[Corresponding to PCT/JP99/04483

Filed August 20, 1999]

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Please amend the above-identified application as follows:

IN THE CLAIMS:

Claim 3, line 2, delete "or 2".

Claim 4, line 2, delete "or 2".

Claim 5, line 2, delete "or 2".

Please add the following new claims:

--9. The aqueous liquid pharmaceutical composition according to claim 2, where the composition is in the form of eye drops.

10. The aqueous liquid pharmaceutical composition according to claim 2, where the composition is in the form of ear drops.

11. The aqueous liquid pharmaceutical composition according to claim 2, where the composition is in the form of nasal drops.--

R E M A R K S

The foregoing amendments avoid the multiple dependency of original claims 3-5, as a result of which new claims 9-11 have been added to the application.

Respectfully submitted,

Shinichi YASUEDA et al.

By



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April 21, 2000

THE COMMISSIONER IS AUTHORIZED
TO CHARGE ANY DUE
FEE FOR THIS PAPER TO APPLICANT'S
ACCOUNT NO. 26-0975.

DESCRIPTION

AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION

5 FIELD OF THE INVENTION

The present invention relates to an aqueous liquid pharmaceutical composition comprising as a main component a quinolone carboxylic acid derivative, Gatifloxacin (chemical nomenclature: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinoline carboxylic acid). Further, the present invention relates to a method for raising corneal permeability of Gatifloxacin, a method for preventing precipitation of Gatifloxacin crystals, and a method for preventing coloration of Gatifloxacin.

15

BACKGROUND OF THE INVENTION

Gatifloxacin is a new quinolone antimicrobial agent which is recognized to exhibit a strong antimicrobial activity against not only Gram-negative bacteria but also Gram-positive bacteria, anaerobes and mycoplasmas. Then, it has been proposed to apply it to ophthalmological infectious diseases such as conjunctivitis, dacryocystitis, hordeolum etc. and otorhinological infectious diseases such as otitis externa, otitis media, sinusitis etc (see JP-B 8-9597).

For designing a pharmaceutical preparation in the form of eye drops containing an antimicrobial agent, an index is to raise corneal permeability of the agent to increase the amount of the agent to transfer to aqueous humor. However, in general, the agent applied to eyes can scarcely pass into inside of the eyes because of dilution with tears and the barrier function of corneas. Then, as a method of improving corneal permeability of the agent, a method using an absorption enhancer has been proposed. In addition, a method using a viscous base material has been proposed to increase the agent-retentivity at the anterior ocular segment.

OBJECTS OF THE INVENTION

With regard to Gatifloxacin, although its application to ophthalmological or otorhinological infectious diseases has been proposed, there is no report about a study of an aqueous liquid pharmaceutical composition thereof for topical administration, which can be actually applied to eyes, for example, its passing into inside of eyes, stability, etc.

In view of these circumstances, an object of the present invention is to permit actual application of Gatifloxacin in ophthalmological or otorhinological field, in particular, to provide an aqueous liquid pharmaceutical composition comprising as an effective component Gatifloxacin.

SUMMARY OF THE INVENTION

The present inventors have intensively studied to apply Gatifloxacin in ophthalmological field and, consequently, have found that this objective can be achieved by coexistence of 5 Gatifloxacin with disodium edetate.

Disodium edetate is considered to lower the calcium concentration in corneal epithelium cells and expanding intercellular spaces, thereby accelerating passing of a water-soluble medicament into inside of eyes. However, a rise in corneal permeability of a medicament depends on a concentration of disodium edetate (Journal of Pharmaceutical Science, 77: 3-14, 1988) and, normally, at present, disodium edetate should be used at a high concentration as much as 0.5% (Investigative Ophthalmology & Visual Science, 26: 110-113, 1985; Experimental Eye Research, 54: 747-757, 10 1992; Pharmaceutical Research, 12: 1146-1150). Nevertheless, the 15 present inventors have found that corneal permeability of Gatifloxacin can be improved at a lower concentration of disodium edetate.

Further, it has been known that the solubility of 20 Gatifloxacin depends on pH and its solubility at about physiological pH is very low. Then, in order to dissolve a sufficient amount of Gatifloxacin in an aqueous liquid pharmaceutical composition, pH of the composition should be adjusted to an acidic or alkaline range, which causes a problem

such as irritation upon topical administration. However, the present inventors also have found that the solubility of Gatifloxacin at about physiological pH is improved by coexistence thereof with disodium edetate.

5 The present invention has been completed based on these present inventors' novel findings and, according to the present invention, there is provided an aqueous liquid pharmaceutical composition which comprises Gatifloxacin or its salt and disodium edetate. In particular, the aqueous liquid pharmaceutical composition of the present invention is an aqueous solution containing Gatifloxacin or its salt and disodium edetate.

10 Further, the present invention provides a method for raising corneal permeability of Gatifloxacin which comprises incorporating disodium edetate into eye drops containing Gatifloxacin or its salt; a method for preventing precipitation of Gatifloxacin crystals which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt; and a method for preventing coloration of Gatifloxacin which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

15 This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description.

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, Gatifloxacin or its salt is used as the effective component. Examples of the salt of Gatifloxacin used in the present invention include those with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, etc.; those with organic acids such as methanesulfonic acid, lactic acid, oxalic acid, acetic acid, etc.; or those with sodium, potassium, magnesium, calcium, aluminum, cerium, chromium, cobalt, copper, iron, zinc, platinum, silver, etc.

Normally, the amount of Gatifloxacin or its salt (hereinafter sometimes simply referred to as "Gatifloxacin") to be formulated in the aqueous liquid pharmaceutical composition of the present invention is varied according to the degree of infection of a particular subject, but normally, Gatifloxacin is formulated within the range of 0.1 to 1.0 w/v%, preferably 0.1 to 0.8 w/v%, more preferably 0.3 to 0.5 w/v%.

Normally, disodium edetate is formulated in an amount of 0.001 to 0.2 w/v%, preferably 0.005 to 0.1 w/v%, more preferably 0.01 to 0.1 w/v%.

Normally, the aqueous liquid pharmaceutical composition of the present invention is adjusted to pH 5 to 8, preferably pH 5.5 to 7.5, more preferably pH 6 to 7.

If necessary, the aqueous liquid pharmaceutical

composition of the present invention may further contain appropriate additives, for example, an isotonic agent (e.g., sodium chloride, potassium chloride, boric acid, glycerin, propylene glycol, mannitol, sorbitol, glucose etc.); a buffer solution (e.g., phosphate buffer solution, acetate buffer solution, borate buffer solution, citrate buffer solution, glutamic acid, ϵ -aminocapronic acid, etc.); a preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, p-hydroxybenzoate, etc.), a thickening agent (e.g., methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, sodium hyaluronate, carboxyvinyl polymer, polyvinyl alcohol, polyvinyl pyrrolidone, Macrogol (polyethylene glycol), etc.), a pH adjusting agent (e.g., hydrochloric acid, sodium hydroxide, acetic acid, phosphoric acid, etc.), and the like.

The aqueous liquid pharmaceutical composition of the present invention can be produced by a per se known method. For example, it can be produced by the process described in the section of "Ophthalmic Solutions" or "Liquids and Solutions", General Rules for Preparations, The Japanese Pharmacopoeia Thirteenth Edition.

The aqueous liquid pharmaceutical composition of the present invention has antimicrobial activity and can be used for prophylaxis and therapy of blepharitis, hordeolum, dacryocystitis, conjunctivitis, tarsitis, keratitis, corneal ulcer, postoperative

infection, and the like. For this purpose, the composition can be instilled in the eye about three times a day at a dosage of one drop per once. For otitis externa or otitis media, normally, the composition can be instilled in the ear twice a day at a dosage of 6 to 10 drops per once. Further, for sinusitis, normally, the composition can be sprayed and inhaled three times every other day in a week at a dosage of 2 to 4 ml per once, or can be administered in the maxillary sinus once a week at a dosage of 1 ml per once.

5 The dosage can be increased or decreased according to the degree of a particular disease condition.

10 The present invention will be further illustrated by the following experiments and examples, but the present invention is not limited thereto.

Experiment 1

15 Effect of disodium edetate on transfer of Gatifloxacin to aqueous humor

Method

According to the formulations of Table 1, eye drops of Gatifloxacin were prepared (formulations A-C). Each of the eye drops (50 µl/eye) was instilled once in the eyes of male Japanese albino rabbits (body weight: about 2 kg). At one hour after the instillation, the aqueous humor was collected and the Gatifloxacin concentration was determined by HPLC.

Table 1

Formulations	A	B	C
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	-	-	0.05 g
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	7.0	6.0	6.0

Results

The concentration of Gatifloxacin in the aqueous humor at one hour after the instillation is shown in Table 2.

When pH dropped, the amount of Gatifloxacin transferred to the aqueous humor decreased. For the formulation adjusted to pH 6.0 (formulation C), the amount of Gatifloxacin transferred to the aqueous humor increased by about 1.2 times and 1.5 times as much as those of the formulations A (pH 7.0) and B (pH 6.0) which were used as controls, respectively.

Since the concentration of disodium edetate normally used for raising corneal permeability is 0.5 w/v%, these results show that corneal permeability of Gatifloxacin has been improved even by using disodium edetate in 1/10 amount as much as that normally used.

Table 2

Formulations	Gatifloxacin concentration in aqueous humor ($\mu\text{g}/\text{ml}$)
A	1.61 \pm 0.43
B	1.30 \pm 0.42
C	1.93 \pm 0.95

Experiment 2

Effect of disodium edetate on precipitation of

5 Gatifloxacin crystals

Method

According to the formulations of Table 3, aqueous liquid preparations of Gatifloxacin were prepared (formulations B-D).

10 Each solution was filled in 5 ml glass ampoules. The ampoules were subjected to freezing at -30°C (overnight) and then thawing at room temperature repeatedly to observe precipitation of Gatifloxacin crystals.

Table 3

Formulations	B	C	D
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	-	0.05 g	0.1 g
Sodium chloride	0.9 g	0.9 g	0.9 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	6.0	6.0	6.0

15 Results

In the formulation in which disodium edetate was not formulated (formulation B), crystals were precipitated when

freezing and thawing were repeated twice to three times. On the other hand, when disodium edetate was formulated (formulations C and D), no precipitation of crystals was recognized even when freezing and thawing were repeated ten times.

5 These results show that precipitation of Gatifloxacin crystals under storage conditions at a low temperature is prevented by formulating disodium edetate in an aqueous liquid preparation of Gatifloxacin.

Experiment 3

10 Effect of disodium edetate on preventing coloration of
Gatifloxacin

Method

15 Sodium chloride (0.86 g) and 0.1 mol/liter hydrochloric acid (5.2 ml) were added to sterilized purified water (80 ml) in a stainless steel (SUS316) beaker of 8 cm diameter and the mixture was stirred. Then, Gatifloxacin (0.32 g) and disodium edetate (at a final concentration of 0%, 0.001%, 0.005%, 0.01% or 0.05%) were added thereto and dissolved therein. The solution was adjusted to pH 6.5 with 0.1 mol/liter sodium hydroxide and the total volume
20 was made up to 100 ml to obtain an aqueous liquid preparation of Gatifloxacin. A color difference between the aqueous liquid preparation and sterilized purified water was determined with a differential colorimeter (Chroma meter CT-210C manufactured by Minolta, light source Lab table system). As a control, an aqueous

liquid preparation of Gatifloxacin prepared in a glass beaker was used.

Results

The color difference determined is shown in Table 4.

The aqueous liquid preparation prepared in the glass beaker and used as the control had the color difference of 1.9 to 2.0 and a pale yellow color. On the other hand, the aqueous liquid preparation prepared in the stainless steel beaker had the color difference of 3.17 in case that disodium edetate was not added and 2.42 in case that 0.01% of disodium edetate was added. They had a light yellow color and a pale yellow color, respectively. Thus, they were discolored by formulating disodium edetate.

In view of these results, it is considered that Gatifloxacin is colored by the metal ion dissolved in the preparation from the stainless steel beaker. Further, these results show that addition of disodium edetate can prevent coloration of Gatifloxacin.

Table 4

Concentration of disodium edetate (%)	Color Difference	
	Stainless Steel Beaker	Glass Beaker
0	3.17	1.90
0.001	3.08	1.93
0.005	3.05	2.02
0.01	2.42	1.94
0.05	2.19	1.93

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
5	Gatifloxacin	0.5 g
	Disodium edetate	0.1 g
	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
10	Sterilized purified water	up to 100 ml
	pH	7.0

Example 2

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
	Gatifloxacin	0.5 g
	Disodium edetate	0.05 g
	Sodium chloride	0.9 g
20	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	sterilized purified water	up to 100 ml
	pH	7.0

Example 3

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
5	Gatifloxacin	0.5 g
	Disodium edetate	0.1 g
	Sodium dihydrogen phosphate	0.1 g
	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
10	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	7.0

Example 4

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
	Gatifloxacin	0.3 g
	Disodium edetate	0.05 g
20	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	6.0

Example 5

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
5	Gatifloxacin	0.5 g
	Sodium edetate	0.01 g
	Glycerin	2.6 g
	Benzalkonium chloride	0.005 g
10	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	7.5

Example 6

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
15	Gatifloxacin	0.5 g
20	Sodium edetate	0.05 g
	Sodium chloride	0.9 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml

pH	5.5
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Example 7

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following
5 formulation was prepared.

	Ingredients	Amount
	Gatifloxacin	0.3 g
	Disodium edetate	0.05 g
	Sodium chloride	0.9 g
10	Hydroxypropylmethyl cellulose	0.1 g
	Methyl p-hydroxybenzoate	0.026 g
	Propyl p-hydroxybenzoate	0.014 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
15	Sterilized purified water	up to 100 ml
	pH	6.0

Example 8

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following
20 formulation was prepared.

	Ingredients	Amount
	Gatifloxacin	0.5 g
	Disodium edetate	0.01 g
	Sodium chloride	0.83 g

	Benzalkonium chloride	0.005 g
	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
5	pH	5.5

Example 9

According to a conventional method, an aqueous solution for eye drops, ear drops and nasal drops having the following formulation was prepared.

	Ingredients	Amount
10	Gatifloxacin	0.3 g
	Disodium edetate	0.01 g
	Sodium chloride	0.86 g
	Benzalkonium chloride	0.005 g
15	Hydrochloric acid	q.s.
	Sodium hydroxide	q.s.
	Sterilized purified water	up to 100 ml
	pH	6.0

As shown in Experiment 1, according to the eye drops of the present invention, corneal permeability of the effective component, Gatifloxacin, can be improved even by using disodium edetate in 1/10 amount as much as that normally used. Further, as shown in Experiment 2, the aqueous liquid preparation of the present invention can prevent precipitation of Gatifloxacin

crystals under storage conditions as a low temperature. Furthermore, as shown in Experiment 3, coloration of Gatifloxacin by a metal ion can be prevented. Thus, the aqueous liquid preparation of the present invention is very useful.

CLAIMS

1. An aqueous liquid pharmaceutical composition which
5 comprises Gatifloxacin or its salt and disodium edetate.

2. The aqueous liquid pharmaceutical composition
according to claim 1, wherein pH of the composition is within the
range of 5 to 8.

3. The aqueous liquid pharmaceutical composition
according to claim 1 or 2, where the composition is in the form
of eye drops.

4. The aqueous liquid pharmaceutical composition
according to claim 1 or 2, where the composition is in the form
of ear drops.

5. The aqueous liquid pharmaceutical composition
according to claim 1 or 2, where the composition is in the form
of nasal drops.

6. A method for raising corneal permeability of
Gatifloxacin which comprises incorporating disodium edetate into
20 eye drops containing Gatifloxacin or its salt.

7. A method for preventing precipitation of
Gatifloxacin crystals which comprises incorporating disodium
edetate into an aqueous liquid preparation containing Gatifloxacin
or its salt.

8. A method for preventing coloration of Gatifloxacin which comprises incorporating disodium edetate into an aqueous liquid preparation containing Gatifloxacin or its salt.

ABSTRACT

There is provided an aqueous liquid pharmaceutical
5 composition which comprises Gatifloxacin (chemical nomenclature:
 (\pm) -1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-
1-piperazinyl)-4-oxo-3-quinoline carboxylic acid) or its salt and
disodium edetate. Further, there are provided a method for raising
corneal permeability of Gatifloxacin, a method for preventing
precipitation of Gatifloxacin crystals, and a method for preventing
10 coloration of Gatifloxacin by incorporating disodium edetate into
an aqueous liquid preparation containing Gatifloxacin or its salt.

DECLARATION AND POWER OF ATTORNEY FOR U.S. PATENT APPLICATION

Original Supplemental Substitute PCT Design

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title: AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION

of which is described and claimed in:

(the attached specification, or
 (the specification in the application Serial No. _____ filed _____;
 and with amendments through _____ (if applicable), or
 (the specification in International Application No. PCT/JP99/04483, filed August 20, 1999, and as amended
 on _____ (if applicable).

I hereby state that I have reviewed and understand the content of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge my duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim priority benefits under Title 35, United States Code, §119 (and §172 if this application is for a Design) of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NO.	DATE OF FILING	PRIORITY CLAIMED
Japan	235432/1998	August 21, 1998	YES

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

APPLICATION SERIAL NO.	U.S. FILING DATE	STATUS: PATENTED, PENDING, ABANDONED

(7) And I hereby appoint John T. Miller, Reg. No. 21,120; Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Jeffrey Nolton, Reg. No. 25,408; Warren M. Cheek, Jr., Reg. No. 33,367; Nils E. Pedersen, Reg. No. 33,145 and Charles R. Watts, Reg. No. 33,142, who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., attorneys to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith.

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from Aoyama & Partners as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

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I further declare that all statements made herein of my own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1st Inventor Shinichi Yasaeda Date March 16, 2000
 2nd Inventor Katsuhiko Inada Date March 16, 2000
 3rd Inventor _____ Date _____
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 6th Inventor _____ Date _____
 7th Inventor _____ Date _____

The above application may be more particularly identified as follows:

U.S. Application Serial No. _____ Filing Date _____
 Applicant Reference Number _____ Atty Docket No. _____
 Title of Invention AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION